EXCLI Journal 2023;22:315-328 – ISSN 1611-2156
Received: February 02, 2023, accepted: February 21, 2023, published: February 28, 2023

Letter to the editor:

RECENT STUDIES ON BERBERINE AND ITS BIOLOGICAL AND PHARMACOLOGICAL ACTIVITIES

Priscilla Nadalin[1,†], Yong-Goo Kim[2,†], Sang Un Park[1*]

[1] Department of Crop Science, Chungnam National University, 99 Daehak-ro, Yuseong-gu, Daejeon, 34134, Korea
[2] Department of Herbal Crop Research, National Institute of Horticultural and Herbal Science, RDA, Eumseong 27709, Korea

* **Corresponding author:** Sang Un Park, Department of Crop Science, Chungnam National University, 99 Daehak-ro, Yuseong-gu, Daejeon, 34134, Korea. Tel.: +82-42-821-5730, Fax: +82-42-822-2631, E-mail: supark@cnu.ac.kr

† These authors contributed equally to this work.

https://dx.doi.org/10.17179/excli2023-5898

Benzylisoquinoline alkaloids (BIAs) are a variety of plant chemicals that consist of roughly 2,500 known compounds. Many BIAs are characterized by potent pharmacological activities, notably the narcotic analgesics morphine and codeine, the antimicrobials sanguinarine and berberine, the muscle relaxants (+)-tubocurarine and papaverine, and the cough suppressant and anticancer drug noscapine. A number of medicines that have been known to humankind since ancient times are plant-derived BIAs (Hagel and Facchini, 2013).

Berberine (BBR), a yellowish crystalline benzylisoquinoline alkaloid, is an active compound found in several plants. BBR has been used in traditional Chinese medicine for a long time to treat several conditions (Zhu et al., 2022). BBR alkaloids are found in the leaves, bark, twigs, rhizomes, roots, and stems of plants, with bark and roots containing reasonably high amounts of BBR in comparison to other plant parts (Andola et al., 2010). BBR is a tetracyclic ring system consisting of an N-benzyltetrahydroisoquinoline core with an incorporated additional C13 carbon bridge, which is formed through an oxidative step where the N-methyl group is provided by S-adenosyl methionine to an iminium ion, with a consequent cyclization into an aromatic ring through the phenolic hydroxyl. Starting from tyrosine, BBR biosynthesis consists of 13 stages in which various enzymatic reactions are involved (Singh et al., 2021).

BBR has been reported to be useful for a wide range of biological and pharmacological activities, including antioxidant, anti-inflammatory, anticancer, antimicrobial, antidepressant, hepatoprotective, hypolipidemic, and hypoglycemic activities (Almatroodi et al., 2022; Behl et al., 2022; Cheng et al., 2022; Och et al., 2022; Yarmohammadi et al., 2022; Mohammadian Haftcheshmeh and Momtazi-Borojeni, 2021). Interestingly, many studies have provided evidence suggesting that BBR is a valuable drug candidate with a wide range of therapeutic uses (Mujtaba et al., 2022). Here, we report a summary of the current literature available on the biological and pharmacological activities of BBR (Table 1).

EXCLI Journal 2023;22:315-328 – ISSN 1611-2156
Received: February 02, 2023, accepted: February 21, 2023, published: February 28, 2023

Table 1: Recent studies on the biological and pharmacological activities of berberine

Key findings	Reference
BBR may regulate cellular oxidative stress, apoptosis and autophagy by inducing Camk1db m6A methylation through the targeting of the Camk1db/ERK pathway in zebrafish-hepatocyte.	Zhang et al., 2022a
BBR promotes epithelial repair in experimental colitis by acting on the resident stromal cells and intestinal stem cells and Wnt-β-Catenin signaling could become an interesting target for treating colitis.	Luo et al., 2022
BBR activates the anti-oxidant kelch like ECH associated protein 1 (Keap1)/nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase 1 pathway, leading to elimination of cholesterol overload-induced oxidative stress as well as apoptosis in hepatocytes of mice. These results indicate that BBR could find application as a novel compound for treating cholesterol overload-induced cardiovascular pathologies.	Ye et al., 2022
BBR can lower glucose levels, which is reflected by the baseline fasting plasma glucose and glycosylated hemoglobin levels in patients. BBR treatment could be safe as it does not increment the incidence of total adverse events and the risk of hypoglycemia.	Xie et al., 2022
BBR prevents lethal neurological infection caused by Enterovirus 71 (EV71) by inhibiting virus replication through the regulation of the Keap-Nrf2 axis and reactive oxygen species (ROS) generation in astrocytes of brainstem, hence providing a potential antiviral treatment for severe EV71 infection causing neurological complications.	Cui et al., 2022
Bitter-taste receptors (TAS2Rs) and Gα-gustducin/Gβ1γ13 signaling pathway was identified and functionally characterized. Such signaling pathway is used by tuft cells of obese mice that respond to orally-administered BBR and is a novel mechanism showing the anti-obesity activity of BBR.	Sun et al., 2022
BBR in low doses can suppress epithelial-mesenchymal transition (EMT) and thus cholangiocarcinoma (CCA) cells' aggressiveness, partly due to its multi-kinase inhibiting property on epidermal growth factor receptor and its downstream pathways. Hence, BBR could be useful for treating human CCA.	Obchoei et al., 2022
BBR treatment alleviates ow shear stress-induced vascular endothelial inflammation by reducing the Protein kinase B (Akt)/Interferon regulatory factor 3 signaling pathway activation.	Lv et al., 2022
BBR can improve pulmonary inflammation in mice affected by influenza viral pneumonia by inhibiting the activation of nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome, along with inhibition of Gasdermin D (GSDMD)-mediated pyroptosis through lowered GSDMD expression and inhibited activation of the NLRP3 inflammasome-mediated GSDMD.	An et al., 2022
BBR has shown great efficacy in controlling adipogenesis, inflammation, hyaluronan synthesis, and fibrosis in orbital fibroblasts, suggesting a potential therapeutic role in the treatment of thyroid-associated ophthalmopathy.	Diao et al., 2022
Estrogen receptor (ER)-α36 is implicated in BBR's tamoxifen (TAM)-sensitizing activity on ER-positive breast cancerous cells. These results offer additional insights regarding BBR's usage in cancer TAM co-treatment.	Pan et al., 2022
BBR has a protective effect against oxidative injury induced by sodium nitrite in rat erythrocytes in a dose-dependent manner, which can be possibly reflected in the antioxidant ability of the compound.	Akhzari et al., 2022

Key findings	Reference
BBR can prevent or assist in treating diabetic retinopathy symptoms, with its main protective activity probably involving regulation of the retinal ganglion cells apoptosis through the GABA-alpha receptor/protein kinase C-alpha pathway.	Fang et al., 2022
BBR has been proven effective as a defense against diclofenac sodium-induced testicular dysfunction through an improved oxidant/anti-oxidant balance and the interruption of the apoptotic cascade.	Waly et al., 2022
BBR may alleviate diabetic atherosclerosis by enhancement of the interplay between Hepatic Krüppel-like factor 16 (KLF16) and peroxisome proliferator-activated receptor alpha (PPARα), indicating KLF16 could be a new BBR target and suggesting that the enhancement of KLF16 due to BBR can be a valuable approach in the treatment of diabetic atherosclerosis.	Man et al., 2022
BBR can inhibit ferroptosis by suppressing ROS generation and lowering lipid peroxidation in erastin and Ras-selective lethal small molecule 3-treated cardiac cells.	Yang et al., 2022
BBR can be a valuable treatment modality for obesity and its related metabolic dysfunctions, by modulation of adipose tissue macrophage recruitment and polarization through inhibition of chemotaxis.	Noh et al., 2022
In rats suffering from diet-induced obesity, vasoconstriction and relaxation in mesenteric arterioles are altered, nitric oxide is increased, and noradrenaline is decreased in mesenteric perivascular adipose tissue (PVAT). All such pathological changes can be reversed by BBR, suggesting a novel effect of BBR in mitigating mesenteric vascular dysfunction through regulation of PVAT.	Wang et al., 2022
BBR attenuates 3-nitropropionic acid and haloperidol-induced behavioral changes in rodents, as well as improving their antioxidant capacity. Thus, BBR could become a new strategy for treating Huntington's disease and Tardive dyskinesia.	Kadir et al., 2022
BBR promotes autophagic cell death through inactivation of the Akt/mTOR signaling pathway in melanoma cells: thus it could be a valuable base for the development of anti-melanoma drugs.	Park et al., 2022
BBR may have an inhibiting effect on colon cancer through regulation of the tricarboxylic acid cycle and glycolysis/gluconeogenesis due to its effect on c-MYC and hypoxia-inducible factor 1-alpha (HIF1α) G-quadruplexes.	Wen et al., 2022
BBR can substantially lower the expression of hub gene HEY2 and metastasis-linked proteins E-cadherin and β-catenin and Cyclin D1 involved in MET in colorectal cancer metastasis of the lung and the liver.	Ni et al., 2022b
BBR can bind to the intercellular section of transforming growth factor-β receptor 1 (TGFBR1), inhibit its enzymatic activity, and lower endothelial barrier disruption by tumor cells that exhibit greater levels of TGF-β1. Therefore, BBR could be an interesting candidate for the treatment of pancreatic cancer lung metastasis in clinical practice.	Tian et al., 2022
BBR is effective in ameliorating colorectal carcinogenesis associated with colitis on three levels: 1. Pathogenic and beneficial bacteria; 2. Short-chain fatty acids and Lipopolysaccharide produced by intestinal microflora; 3. Inflammatory tumoral modification signaling and intestine barrier function.	Yan et al., 2022
BBR can suppress lipogenesis by promoting promyelocytic leukemia zinc finger-induced sterol-regulatory element-binding proteins cleavage-activating protein ubiquitination, hence having an inhibiting effect on colon cancer cell metastasis.	Liu et al., 2022

EXCLI Journal 2023;22:315-328 – ISSN 1611-2156
Received: February 02, 2023, accepted: February 21, 2023, published: February 28, 2023

Key findings	Reference
BBR protects islet β cells from injury induced by palmitate, and such protective effect could be obtained by regulating mitophagy. BBR could become a new treatment for β cell injury in diabetes mellitus (DM).	Li et al., 2022
BBR can exert effects on rapamycin's mammalian target, mitogen-activated protein kinase, apoptotic pathway and growth arrest-specific transcript 5 in coronary heart disease, which could influence the healing process.	Han et al., 2022
BBR may inhibit high glucose-induced EMT and renal interstitial fibrosis through suppression of the NLRP3 inflammasome. BBR has the potential to become a novel drug to treat tubulointerstitial fibrosis in diabetic kidney disease.	Ma et al., 2022
BBR shows therapeutic potential by exerting its activity on calcium-mediated signals and the endothelial NLRP3 inflammasome in inflammation-induced vascular damage.	Dai et al., 2022
BBR has outstanding anti-methicillin-resistant Staphylococcus aureus properties in addition to synergetic antibacterial activity when co-administered with either clindamycin or rifamycin, owing to its effects on the destruction of cell walls and membranes.	Xia et al., 2022
BBR administration causes autophagy, and this has a neuroprotective effect on chlorpyrifos-induced apoptosis of developing neurons in Wistar rats F1 generation through regulation of the autophagy-apoptosis equilibrium.	Seth and Chopra, 2022
BBR lowers the inflammatory marker' count and suppresses valve interstitial cells osteogenic differentiation, which could be linked to the Smad1/5/8 and nuclear factor-κB (NF-κB) signaling pathways' inhibition.	Huang et al., 2022
BBR shows an anti-ischemia-reperfusion (I/R) activity in the heart by induction of the miR-26b-5p and suppression of the PTGS2/MAPK pathway. Such data suggest that BBR could be valuable in treating I/R.	Jia et al., 2022
BBR inhibits the inflammatory response caused by lipopolysaccharides through regulation of the NF-κB/Nlrp3 signaling pathway, thus proving it can be a potential compound for the treatment of acute lung injury.	Chen et al., 2022
Pre-administration of BBR can act as prevention of colon carcinogenesis, and the mechanisms behind these effects are related to the inhibited inflammation as well as lowered tumor growth and the maintenance of intestinal homeostasis.	Deng et al., 2022
BBR ameliorates diabetic renal tubulointerstitial injury by improving reduction of fatty acid oxidation induced by high glucose, alleviates lipid deposition, and protects mitochondria in tubular epithelial cells.	Rong et al., 2022
BBR inhibits the phosphorylation of intestine's insulin-like growth factor 1 (IGF-1R), therefore reducing the membrane's localization of PLC-β2, finally inducing lowered translocation of glucose transporter 2 (GLUT2). Such findings hint that BBR can reduce glucose absorption in the intestine via inhibition of the IGF-1R-PLC-β2-GLUT2 signal pathway.	Zhang et al., 2022b
BBR exerts an anti-epileptic activity by regulating some epigenetic, transcription factors & inflammatory biomarkers in a mice model of epilepsy.	Ghanem et al., 2021
BBR can modulate gut flora and metabolism in subjects affected by schizophrenia or bipolar disorder and moderate olanzapine-induced metabolic perturbations.	Pu et al., 2021
BBR is a promising anti-autophagy and apoptosis agent which may increase the survival rate of adipose-derived mesenchymal stem cells during cell transplantation.	Pang et al., 2021

Key findings	Reference
BBR has proven effective in decreasing m6A methylation by lowering β-catenin and subsequently increasing fat mass and obesity-associated protein, suggesting a role of BBR in the modulation of stemness and malignant behaviors in colorectal cancer stem cells.	Zhao et al., 2021
BBR ameliorates the condition of fibrotic liver by leading ferrous redox to initiate ROS-mediated ferroptosis of hepatic stellate cells. As such, BBR could be an interesting new compound for fibrotic liver treatment.	Yi et al., 2021
BBR possesses a wide range of pharmacological activities that can be studied to understand its aptness as an alternative neuroprotective compound against developmental neurotoxicity induced by lactational exposure to chlorpyrifos.	Seth et al., 2021
BBR's antiproliferative activity in HepG2 cells leads to apoptosis as well as cell cycle arrest. BBR as a regulator of the AKAP12 signaling may be a novel strategy for hepatocellular carcinoma treatment.	Yang et al., 2021
BBR ameliorates colitis induced by dextran sulfate sodium. It may regulate intestinal immune cell differentiation through its activity on the growth of Bacteroides fragilis, providing novel insights into BBR potential applications in ulcerative colitis (UC).	Zheng et al., 2021a
BBR can ameliorate steatosis induced by free fatty acid in HepG2 cells via activation of the silent information regulator 1 (SIRT1)-forkhead box transcription factor O1-sterol regulatory element-binding protein 2 signal pathway. Thus, BBR could become a novel compound for the treatment of nonalcoholic liver steatosis.	Shan et al., 2021
BBR can affect cartilage differentiation and such novel pharmacological activity should be considered for the design of new clinical protocols aimed at treating degenerative conditions of the cartilage.	Duarte-Olivenza et al., 2021
BBR ameliorates non-alcoholic steatohepatitis via modulation of gastrointestinal microbiota and bile acid metabolism's interaction, and also via the resulting activation of intestinal farnesoid X receptor.	Shu et al., 2021
BBR lowers the risk of choline diet-induced arterial thrombosis by modifying the composition of the gut microbiota and lowering trimethylamine N-oxide generation.	Xie et al., 2021
BBR has a strong protective activity against symptoms of neonatal sepsis in newborn mice, with such effects being dependent on the upregulation of miR-132-3p.	Li et al., 2021
BBR has proven effective in ameliorating the pathological condition in polycystic ovary syndrome (PCOS) via regulation of the gut microbiotas and metabolites. Hence, BBR may become a candidate for the treatment of PCOS-insulin resistance.	Shen et al., 2021
BBR administration can ameliorate fatty liver, by reversing the abnormal expression of microsomal triglyceride transfer protein and low-density lipoprotein receptor and through an inhibition of lipid synthesis.	Chen et al., 2021
BBR improves myocardial I/R injury in male rats by interfering with inflammatory reactions and apoptosis caused by I/R injury.	Abdulredha et al., 2021
BBR suppresses non-small cell lung cancer (NSCLC) cellular proliferation by inhibiting DNA repair and replication rather than inducing apoptosis. Thus, BBR may find valuable use in NSCLC treatment.	Ni et al., 2022a

Key findings	Reference
BBR can selectively activate peroxisome proliferator-activated receptor gamma (PPARγ) to induce a remodeling of fat tissue as well as thermogenesis, by enhancing the AMPK/SIRT1 pathway. Thus, BBR could be a useful agent for obesity treatment.	Xu et al., 2021
BBR's neuroprotective potential lies in its cholinergic, anti-oxidative, genoprotective, anti-inflammatory, and anti-apoptotic properties. Results suggest that BBR could be an interesting pre-clinical neuroprotective compound, acting against doxorubicin-induced neurotoxicity during cancer treatment.	Ibrahim Fouad and Ahmed, 2021
BBR can regulate deoxynivalenol-induced intestinal injury, immunosuppression and oxidative stress through regulation of the NF-κB and MAPK signaling pathways, thus helping in maintaining the intestinal health of piglets.	Tang et al., 2021
BBR has the potential to alleviate two major pathological manifestations of Alzheimer's disease (AD) essentially by suppressing endoplasmic reticulum stress. BBR could thus be the starting point to obtain novel compounds for AD treatment.	Wu et al., 2021
Diet BBR protection against cardiac disorders in gestational DM-exposed mice offspring is related to ameliorated mitochondrial function, due to incremented cardiolipin production.	Cole et al., 2021
BBR has protective effects against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine toxicity and this may be ascribed to BBR-enhanced autophagy via the AMPK-dependent pathway.	Deng and Ma, 2021
BBR has the potential to activate miR-192 expression, downregulate PPARγ expression as well as lipid synthesis-related genes' expression, increase PPARγ phosphorylation, and lower c-Jun-N-terminal kinase phosphorylation to enhance lipid metabolism, which is useful to increase the grade of in vitro maturation of porcine oocyte.	Dai et al., 2021
BBR can alter UC by impacting inflammation- and immunity-related biological processes and signal pathways. Further study of its mechanism of action on UC will likely generate useful data for clinical practice.	Jiang et al., 2021
BBR can ameliorate the liver's resistance to insulin via the miR-146b/sirtuin 1 pathway, which could act as a potential therapeutic target for preventing and treating metabolic pathologies, especially diabetes.	Sui et al., 2021
BBR represses mitochondrial complex I in the gut and liver, which leads to an inhibited lipid metabolism and ultimately to a mitigation of fatty liver and obesity, with such activity being unrelated to intestinal bacteria.	Yu et al., 2021
BBR treatment can inhibit Protein kinase RNA-like endoplasmic reticulum kinase/eukaryotic translation initiation factor-2α signaling-mediated β-site APP cleavage enzyme 1 translation, therefore lowering β-amyloid synthesis and consequent neuronal apoptosis. In addition, BBR possesses neuroprotective activity, expressed by attenuation of ER stress and oxidative stress. Hence, BBR could be valuable for the treatment of AD.	Liang et al., 2021
BBR can effectively ameliorate both obesity and hyperlipidemia by lowering triglyceride, total cholesterol, and low-density lipoprotein and incrementing high-density lipoprotein; in addition, BBR can improve Type II diabetes by lowering insulin resistance and can prevent diabetic encephalopathy (DE).	Ye et al., 2021

Key findings	Reference
BBR may revert macrophage function in cancerous tissue, increase rituximab-induced phagocytosis and stimulate anti-CD47 antibody activity by suppressing CD47 expression, thus providing a novel insight on BBR's anti-tumor mechanism of action and supplying new information regarding immunochemotherapy with rituximab and CD47-targeted immunotherapy in diffuse large B-cell lymphoma.	Ren et al., 2021
BBR may influence the expression of parvalbumin in hippocampal neurons. BBR may be responsible for the modulation of Ca^{2+} levels in neurons and therefore potentially have a neuroprotective activity against neuronal damages.	Szalak et al., 2021
BBR prevents DR development by modulation of the glucolipid metabolism and inhibition of the HIF-1α/vascular endothelial growth factor/NF-κB pathway. Therefore, BBR could be a potential treatment of DR.	Yin et al., 2021
BBR can act as a potential prophylactic addition for rheumatoid arthritis, mainly by suppressing T cells. Nonetheless, because of the cells involved, there are concerns over BBR prophylactic utilization regarding vaccine efficacy and other immune responses.	Vita et al., 2021
BBR promotes allograft survival by inducing alloreactive T cells' apoptosis. Results provide additional evidence in favor of the potential use of BBR in translational medicine.	Ma et al., 2021
A new mechanism implied in BBR's pharmacological activity is related to a donor-specific memory T-cell generation correlated to a particular pathogen. Such results may be valuable in blocking rejection of human transplants given that BBR is already in use for the treatment of intestinal infections.	Qiu et al., 2021
BBR stimulates autophagy of peritoneal macrophages through activation of SIRT1 via the nicotinamide adenine dinucleotide (NAD+) synthetic pathway and, in turn, promotion of the transcription factor EB (TFEB) nuclear translocation and deacetylation. The functional regulation of SIRT1 and TFEB induced by BBR could lead to a potential therapeutic strategy for atherosclerosis' treatment.	Zheng et al., 2021b
BBR increases mitochondria membrane potential and reduces ROS in rats with DE via inhibition of the Rho/ROCK pathway. Such results could provide new insights for DE management.	Tian et al., 2021
BBR is a tyrosine hydroxylase agonist in Enterococcus and may stimulate gut L-dopa production. In addition, results from 28 hyperlipidemia patients provided additional proof that BBR administered per os increases blood/fecal L-dopa via action of the intestinal bacteria. Therefore, BBR could ameliorate brain activity with a vitamin-like effect, via upregulation of L-dopa biosynthesis in the gastrointestinal microflora.	Wang et al., 2021
BBR inhibits the activation of NLRP3 inflammasome and restores autophagic activity acting as a protector of dopaminergic neurons against both *in vivo and in vitro* degeneration, thus designating BBR as an interesting compound for the treatment of Parkinson's disease.	Huang et al., 2021
BBR has a protective activity against diet-induced heart structural dysfunctions and defective mitochondria related to cardiac Kruppel-like factor 4 (KLF4) signaling. Cardiac KLF4 is among the potential targets for the treatment of heart tissue damages caused by obesity.	Ding et al., 2021
A 600 mg/kg BBR supplementation could positively impact growth, hepatic activity, and antioxidant status in broilers subjected to feed adulterated with aflatoxin B1 and ochratoxin A.	Malekinezhad et al., 2021

EXCLI Journal 2023;22:315-328 – ISSN 1611-2156
Received: February 02, 2023, accepted: February 21, 2023, published: February 28, 2023

Key findings	Reference
Dietary BBR addition improves yellow-feathered broilers' growth, and is correlated to relevant modifications in the composition of cecal microflora.	Zhu et al., 2021
BBR may improve glucose metabolism of Megalobrama amblycephala by enhancing glycolysis in the liver and insulin signaling, along with preventing liver's glycogen synthesis and gluconeogenesis. Results additionally suggest that BBR may lower the liver metabolic burden via inhibition of fat synthesis and promotion of lipid decomposition and may as well improve fat uptake in peripheral tissues.	He et al., 2021
BBR provides neuroprotection against doxorubicin-induced cognitive decline via modulation of brain growth factors and its anti-inflammatory, anti-apoptotic and anti-oxidative activities.	Shaker et al., 2021
BBR effects on bile acids in the gut could lead to specific pharmaceutical interventions.	Wolf et al., 2021
BBR positively inhibits alveolar bone loss and inflammation in rats affected by ligature-induced periodontitis, and such activity is related to the inhibition of the activity of the P38MAPK/NF-κB pathway, which is mediated by the G Protein-coupled ER.	Gu et al., 2021
BBR positively affects the advancement of osseointegration in DM by targeting ROS-mediated insulin receptor substrate-1 signaling. Thus, BBR may become a valuable aid for implants restoration in diabetic patients.	Shao et al., 2021
BBR could possess protective activity against podocyte apoptosis caused by palmitic acid, and elimination of ROS-dependent ER stress might be the main reason for BBR protective activity.	Xiang et al., 2021
BBR inhibits colonic phospholipase A2a (PLA2G4A) activity leading to an improvement of colon inflammation in experimental colitic mice, proposing modulation of the phosphatidylcholine metabolism via PLA2G4A as a valuable path to establish novel therapeutic strategies for the treatment of UC.	Zhai et al., 2020b
BBR's bioavailability per os and glucose-lowering activity may be highly accentuated by encapsulation into galactose-mixed micelles. Therefore, galactosylated micelles can be useful material for the development of BBR nanodrugs to treat DM.	Kang et al., 2020
BBR administration has proven very effective in lowering the reproductive toxicity caused by Hg intoxication. Such protective activity is due to its strong antioxidant, anti-inflammatory, and antiapoptotic effects, implying that BBR could be used to ameliorate Hg intoxication-induced reproductive toxicity.	Albasher et al., 2020
BBR can act as a protective agent against oxygen-glucose deprivation/reperfusion-induced apoptosis via regulation of the ER stress and autophagy, and therefore, could potentially be a promising compound for treating cerebral I/R damages.	Xie et al., 2020
BBR has been proven effective on improving glioblastoma (GBM) cells' sensitivity to temozolomide in a way that is reliant on the ERK1/2-mediated autophagy induction, hence suggesting that BBR can potentially be a valuable compound for treatment of GBM.	Qu et al., 2020
BBR ameliorates hyperglycemia, and this effect may be related to the improved deoxycholic acid synthesis by the microbiome, which upregulates colonic Takeda G protein-coupled receptor 5 expression and glucagon-like peptide secretion, and improves glucose, lipid and energy metabolism in db/db mice.	Li et al., 2020

Key findings	Reference
BBR ameliorates damages caused by dexamethasone, such as lowered growth and migration, oxidative stress, and apoptosis in tendon cells via activation of the PI3K/AKT signaling pathway as well as regulation of phenotype-related biomarkers' expression in tendon cells. Nonetheless, additional research is required to shed light on the in vivo protective effects of BBR.	Fu et al., 2020
BBR is able to directly block functions and differentiation of inflammation-inducing T helper (Th) 1 and Th17 cells, and indirectly lower inflammation mediated by Th cells by regulating or inhibiting Tregs, dendritic cells and macrophages' assistive autoreactive inflammation.	Ehteshamfar et al., 2020
BBR has an important role in alleviating heart hypertrophy and preserving its function from heart failure caused by excessive pressure. The possible underlying mechanism may be mitochondrial autophagy activation via the PINK1/Parkin/Ubiquitination pathway.	Abudureyimu et al., 2020
BBR prevents proliferation and migration of osteosarcoma cells and most importantly annuls EMT, in addition to modulating key epigenetic regulators.	Mishra et al., 2020
BBR has a protective activity against DR through inhibition of oxidative stress and cell apoptosis due to blocking the NF-κB signaling pathway; hence, BBR could be a future agent for DR treatment.	Zhai et al., 2020a

Conflict of interest statement

The authors have no conflicts of interest to declare.

Acknowledgments

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2022R1I1A3054240)

REFERENCES

Abdulredha A, Abosaooda M, Al-Amran F, Hadi NR. Berberine protests the heart from ischemic reperfusion injury via interference with oxidative and inflammatory pathways. Med Arch. 2021;75(3):174.

Abudureyimu M, Yu W, Cao RY, Zhang Y, Liu H, Zheng H. Berberine promotes cardiac function by upregulating PINK1/Parkin-mediated mitophagy in heart failure. Front Physiol. 2020;11:565751.

Akhzari M, Barazesh M, Jalili S, Farzinezhadi Zadeh MM. Berberine recovered oxidative stress induced by sodium nitrite in rat erythrocytes. Drug Metab Bioanal Lett. 2022;15:192-201.

Albasher G, Alkahtani S, Alarifi S. Berberine mitigates oxidative damage associated with testicular impairment following mercury chloride intoxication. J Food Biochem. 2020;44(9):e13385.

Almatroodi SA, Alsahli MA, Rahmani AH. Berberine: An important emphasis on its anticancer effects through modulation of various cell signaling pathways. Molecules. 2022;27(18):5889.

An C, Wu Y, Wu J, Liu H, Zhou S, Ge D, et al. Berberine ameliorates pulmonary inflammation in mice with influenza viral pneumonia by inhibiting NLRP3 inflammasome activation and gasdermin D-mediated pyroptosis. Drug Dev Res. 2022;83:1707-21.

Andola HC, Gaira KS, Rawal RS, Rawat MSM, Bhatt ID. Habitat-dependent variations in berberine content of Berberis asiatica Roxb. ex. DC. in Kumaon, Western Himalaya. Chem Biodivers. 2010;7:415-20.

Behl T, Singh S, Sharma N, Zahoor I, Albarrati A, Albratty M, et al. Expatiating the pharmacological and nanotechnological aspects of the alkaloidal drug berberine: current and future trends. Molecules. 2022;27(12):3705.

Chen J, Huang Y, Bian X, He Y. Berberine ameliorates inflammation in acute lung injury via NF-κB/Nlrp3 signaling pathway. Front Nutr. 2022;9:851255.

Chen P, Li Y, Xiao L. Berberine ameliorates nonalcoholic fatty liver disease by decreasing the liver lipid content via reversing the abnormal expression of MTTP and LDLR. Exp Ther Med. 2021;22(4):1109.

Cheng Z, Kang C, Che S, Su J, Sun Q, Ge T, et al. Berberine: a promising treatment for neurodegenerative diseases. Front Pharmacol. 2022;13:845591.

Cole LK, Sparagna GC, Vandel M, Xiang B, Dolinsky VW, Hatch GM. Berberine elevates cardiolipin in heart of offspring from mouse dams with high fat diet-induced gestational diabetes mellitus. Sci Rep. 2021;11(1):15770.

Cui G, Wang H, Yang C, Zhou X, Wang J, Wang T, et al. Berberine prevents lethal EV71 neurological infection in newborn mice. Front Pharmacol. 2022; 13:1027566.

Dai JG, Huang XM, Zhang C, Gao JM. Mechanisms of lipid metabolism promoted by berberine via peroxisome proliferator-activated receptor gamma during in vitro maturation of porcine oocytes. Anim Sci J. 2021;92(1):e13582.

Dai L, Zhu L, Ma S, Liu J, Zhang M, Li J, et al. Berberine alleviates NLRP3 inflammasome induced endothelial junction dysfunction through Ca2+ signalling in inflammatory vascular injury. Phytomedicine. 2022;101:154131.

Deng H, Ma Z. Protective effects of berberine against MPTP-induced dopaminergic neuron injury through promoting autophagy in mice. Food Funct. 2021;12: 8366-75.

Deng J, Zhao L, Yuan X, Li Y, Shi J, Zhang H, et al. Pre-administration of berberine exerts chemopreventive effects in AOM/DSS-induced colitis-associated carcinogenesis mice via modulating inflammation and intestinal microbiota. Nutrients. 2022;14(4):726.

Diao J, Chen X, Mou P, Ma X, Wei R. Potential therapeutic activity of berberine in thyroid-associated ophthalmopathy: inhibitory effects on tissue remodeling in orbital fibroblasts. Invest Ophthalmol Vis Sci. 2022;63(10):6.

Ding L, Li S, Wang F, Xu J, Li S, Wang B, et al. Berberine improves dietary-induced cardiac remodeling by upregulating Kruppel-like factor 4-dependent mitochondrial function. Biol Chem. 2021; 402:795-803.

Duarte-Olivenza C, Montero JA, Lorda-Diez CI. Effects of berberine on the chondrogenic differentiation of embryonic limb skeletal progenitors. J Inflamm Res. 2021;14:5001-11.

Ehteshamfar SM, Akhbari M, Afshari JT, Seyedi M, Nikfar B, Shapouri-Moghaddam A, et al. Anti-inflammatory and immune-modulatory impacts of berberine on activation of autoreactive T cells in autoimmune inflammation. J Cell Mol Med. 2020;24: 13573-88.

Fang W, Huang X, Wu K, Zong Y, Yu J, Xu H, et al. Activation of the GABA-alpha receptor by berberine rescues retinal ganglion cells to attenuate experimental diabetic retinopathy. Front Mol Neurosci. 2022;15: 930599.

Fu S, He Z, Tang Y, Lan B. Effects and mechanism of berberine on the dexamethasone-induced injury of human tendon cells. Evid Based Complement Alternat Med. 2020;2020:8832218.

Ghanem HB, Emam MN, Mohammed ADA, Nagi A-ER. Impact of berberine on some epigenetic, transcription regulation and inflammatory biomarkers in a mice model of epilepsy. Rep Biochem Mol Biol. 2021;10(3):362.

Gu L, Ke Y, Gan J, Li X. Berberine suppresses bone loss and inflammation in ligature-induced periodontitis through promotion of the G protein-coupled estrogen receptor-mediated inactivation of the p38MAPK/NF-κB pathway. Arch Oral Biol. 2021;122:104992.

Hagel JM, Facchini PJ. Benzylisoquinoline alkaloid metabolism: a century of discovery and a brave new world. Plant Cell Physiol. 2013;54(5):647-72.

Han YC, Xie HZ, Lu B, Xiang RL, Li JY, Qian H, et al. Effect of berberine on global modulation of lncRNAs and mRNAs expression profiles in patients with stable coronary heart disease. BMC Genomics. 2022;23(1):400.

He C, Jia X, Zhang L, Gao F, Jiang W, Wen C, et al. Dietary berberine can ameliorate glucose metabolism disorder of Megalobrama amblycephala exposed to a high-carbohydrate diet. Fish Physiol Biochem. 2021; 47:499-513.

Huang Q, He W, Weng Y, Wang Y, Liu Y, Xiang Y, et al. Berberine inhibits osteogenic differentiation of aortic valve interstitial cells by interfering Smad1/5/8 and NF-κB pathways. Vascul Pharmacol. 2022;144: 106986.

Huang S, Liu H, Lin Y, Liu M, Li Y, Mao H, et al. Berberine protects against NLRP3 inflammasome via ameliorating autophagic impairment in MPTP-induced Parkinson's disease model. Front Pharmacol. 2021;11: 618787.

Ibrahim Fouad G, Ahmed KA. Neuroprotective potential of berberine against doxorubicin-induced toxicity in rat's brain. Neurochem Res. 2021;46:3247-63.

Jia X, Shao W, Tian S. Berberine alleviates myocardial ischemia–reperfusion injury by inhibiting inflammatory response and oxidative stress: The key function of miR-26b-5p-mediated PTGS2/MAPK signal transduction. Pharm Biol. 2022;60:652-63.

Jiang Y, Zhao L, Chen Q, Zhou L. Exploring the mechanism of berberine intervention in ulcerative colitis from the perspective of inflammation and immunity based on systemic pharmacology. Evidence Based Complement Alternat Med. 2021;2021: 9970240.

Kadir A, Singh J, Rahi V, Kumar P. Berberine ameliorate haloperidol and 3-Nitropropionic acid-induced neurotoxicity in rats. Neurochem Res. 2022; 47:3285-97.

Kang H, Yao Y, Zhang X. Mixed micelles with galactose ligands for the oral delivery of berberine to enhance its bioavailability and hypoglycemic effects. J Biomed Nanotechnol. 2020;16:1755-64.

Li B, Niu S, Geng H, Yang C, Zhao C. Berberine attenuates neonatal sepsis in mice by inhibiting FOXA1 and NF-κB signal transduction via the induction of MiR-132-3p. Inflammation. 2021;44: 2395-406.

Li M, Zhou W, Dang Y, Li C, Ji G, Zhang L. Berberine compounds improves hyperglycemia via microbiome mediated colonic TGR5-GLP pathway in db/db mice. Biomed Pharmacother. 2020;132:110953.

Li M, She J, Ma L, Ma L, Ma X, Zhai J. Berberine protects against palmitate induced beta cell injury via promoting mitophagy. Genes Genomics. 2022;44:867-78.

Liang Y, Ye C, Chen Y, Chen Y, Diao S, Huang M. Berberine improves behavioral and cognitive deficits in a mouse model of alzheimer's disease via regulation of β-amyloid production and endoplasmic reticulum stress. ACS Chem Neurosci. 2021;12:1894-904.

Liu Y, Fang X, Li Y, Bing L, Li Y, Fang J, et al. Berberine suppresses the migration and invasion of colon cancer cells by inhibition of lipogenesis through modulation of promyelocytic leukemia zinc finger-mediated sterol-regulatory element binding proteins cleavage-activating protein ubiquitination. J Pharm Pharmacol. 2022;74:1353-63.

Luo Z, Li Z, Liang Z, Wang L, He G, Wang D, et al. Berberine increases stromal production of Wnt molecules and activates Lgr5+ stem cells to promote epithelial restitution in experimental colitis. BMC Biol. 2022;20(1):287.

Lv Y, Yang H, Ye P, Qian Z, Wang D, Kong C, et al. Berberine inhibits low shear stress-induced vascular endothelial inflammation via decreasing phosphorylation of Akt and IRF3. Tissue Cell. 2022;79:101946.

Ma Y, Yan G, Guo J, Li F, Zheng H, Wang C, et al. Berberine prolongs mouse heart allograft survival by activating T cell apoptosis via the mitochondrial pathway. Front Immunol. 2021;12:616074.

Ma Z, Zhu L, Wang S, Guo X, Sun B, Wang Q, et al. Berberine protects diabetic nephropathy by suppressing epithelial-to-mesenchymal transition involving the inactivation of the NLRP3 inflammasome. Ren Fail. 2022;44(1):923-32.

Malekinezhad P, Ellestad LE, Afzali N, Farhangfar SH, Omidi A, Mohammadi A. Evaluation of berberine efficacy in reducing the effects of aflatoxin B1 and ochratoxin A added to male broiler rations. Poult Sci. 2021;100:797-809.

Man B, Hu C, Yang G, Xiang J, Yang S, Ma C. Berberine attenuates diabetic atherosclerosis via enhancing the interplay between KLF16 and PPARα in ApoE−/− mice. Biochem Biophys Res Commun. 2022;624:59-67.

Mishra R, Nathani S, Varshney R, Sircar D, Roy P. Berberine reverses epithelial-mesenchymal transition and modulates histone methylation in osteosarcoma cells. Mol Biol Rep. 2020;47:8499-511.

Mohammadian Haftcheshmeh S, Momtazi-Borojeni AA. Berberine as a promising natural compound for the treatment of periodontal disease: A focus on anti-inflammatory properties. J Cell Mol Med. 2021;25: 11333-7.

Mujtaba MA, Akhter MH, Alam M, Ali MD, Hussain A. An updated review on therapeutic potential and recent advances in drug delivery of Berberine: Current status and future prospect. Curr Pharm Biotechnol. 2022;23(1):60-71.

Ni L, Li Z, Ren H, Kong L, Chen X, Xiong M, et al. Berberine inhibits non-small cell lung cancer cell growth through repressing DNA repair and replication rather than through apoptosis. Clin Exp Pharmacol Physiol. 2022a;49(1):134-44.

Ni L, Sun P, Ai M, Kong L, Xu R, Li J. Berberine inhibited the formation of metastasis by intervening the secondary homing of colorectal cancer cells in the blood circulation to the lung and liver through HEY2. Phytomedicine. 2022b;104:154303.

Noh JW, Jun MS, Yang HK, Lee BC. Cellular and molecular mechanisms and effects of berberine on obesity-induced inflammation. Biomedicines. 2022;10 (7):1739.

Obchoei S, Detarya M, Boonnate P, Saranaruk P, Vaeteewoottacharn K, Mahalapbutr P, et al. Low dose berberine suppresses cholangiocarcinoma cell progression as a multi-kinase inhibitor. Asian Pac J Cancer Prev. 2022;23:3379-86.

Och A, Och M, Nowak R, Podgórska D, Podgórski R. Berberine, a herbal metabolite in the metabolic syndrome: The risk factors, course, and consequences of the disease. Molecules. 2022;27(4):1351.

Pan X, Song Z, Cui Y, Qi M, Wu G, Wang M. Enhancement of sensitivity to tamoxifen by berberine in breast cancer cells by inhibiting ER-α36 expression. Iran J Pharm Res. 2022:21(1):e126919.

Pang H, Zhou Y, Wang J, Wu H, Liu X, Gao F, et al. Berberine influences the survival of fat grafting by inhibiting autophagy and apoptosis of human adipose derived mesenchymal stem cells. Drug Des Devel Ther. 2021;15:4795-809.

Park GS, Park B, Lee MY. Berberine induces autophagic cell death by inactivating the Akt/mTOR signaling pathway. Planta Med. 2022;88:1116-22.

Pu Z, Sun Y, Jiang H, Hou Q, Yan H, Wen H, et al. Effects of berberine on gut microbiota in patients with mild metabolic disorders induced by Olanzapine. Am J Chin Med. 2021;49:1949-63.

Qiu F, Lu W, Ye S, Liu H, Zeng Q, Huang H, et al. Berberine promotes induction of immunological tolerance to an allograft via downregulating memory CD8+ T-cells through altering the gut microbiota. Front Immunol. 2021;12:646831.

Qu H, Song X, Song Z, Jiang X, Gao X, Bai L, et al. Berberine reduces temozolomide resistance by inducing autophagy via the ERK1/2 signaling pathway in glioblastoma. Cancer Cell Int. 2020;20(1):592.

Ren S, Cai Y, Hu S, Liu J, Zhao Y, Ding M, et al. Berberine exerts anti-tumor activity in diffuse large B-cell lymphoma by modulating c-myc/CD47 axis. Biochem Pharmacol. 2021;188:114576.

Rong Q, Han B, Li Y, Yin H, Li J, Hou Y. Berberine reduces lipid accumulation by promoting fatty acid oxidation in renal tubular epithelial cells of the diabetic kidney. Front Pharmacol. 2022;12:3926.

Seth E, Ahsan AU, Kaushal S, Mehra S, Chopra M. Berberine affords protection against oxidative stress and apoptotic damage in F1 generation of wistar rats following lactational exposure to chlorpyrifos. Pestic Biochem Physiol. 2021;179:104977.

Seth E, Chopra M. Neuroprotective efficacy of berberine following developmental exposure to chlorpyrifos in F1 generation of Wistar rats: Apoptosis-autophagy interplay. Sci Total Environ. 2022;834:155292.

Shaker FH, El-Derany MO, Wahdan SA, El-Demerdash E, El-Mesallamy HO. Berberine ameliorates doxorubicin-induced cognitive impairment (chemobrain) in rats. Life Sci. 2021;269: 119078.

Shan MY, Dai Y, Ren XD, Zheng J, Zhang KB, Chen B, et al. Berberine mitigates nonalcoholic hepatic steatosis by downregulating SIRT1-FoxO1-SREBP2 pathway for cholesterol synthesis. J Integr Med. 2021; 19:545-54.

Shao J, Liu S, Zheng X, Chen J, Li L, Zhu Z. Berberine promotes peri-implant osteogenesis in diabetic rats by ROS-mediated IRS-1 pathway. Biofactors. 2021;47 (1):80-92.

Shen HR, Xu X, Ye D, Li XL. Berberine improves the symptoms of DHEA-induced PCOS rats by regulating gut microbiotas and metabolites. Gynecol Obstet Invest. 2021;86:388-97.

Shu X, Li M, Cao Y, Li C, Zhou W, Ji G, et al. Berberine alleviates non-alcoholic steatohepatitis through modulating gut microbiota mediated intestinal FXR activation. Front Pharmacol. 2021;12:750826.

Singh S, Pathak N, Fatima E, Negi AS. Plant isoquinoline alkaloids: Advances in the chemistry and biology of berberine. Eur J Med Chem. 2021;226: 113839.

Sui M, Jiang X, Sun H, Liu C, Fan Y. Berberine ameliorates hepatic insulin resistance by regulating microRNA-146b/SIRT1 pathway. Diabetes Metab Syndr Obes. 2021;14:2525-37.

Sun S, Yang Y, Xiong R, Ni Y, Ma X, Hou M, et al. Oral berberine ameliorates high-fat diet-induced obesity by activating TAS2Rs in tuft and endocrine cells in the gut. Life Sci. 2022;311:121141.

Szalak R, Kukula-Koch W, Matysek M, Kruk-Słomka M, Koch W, Czernicka L, et al. Effect of berberine isolated from barberry species by centrifugal partition chromatography on memory and the expression of parvalbumin in the mouse hippocampus Proper. Int J Mol Sci. 2021;22(9):4487.

Tang M, Yuan D, Liao P. Berberine improves intestinal barrier function and reduces inflammation, immunosuppression, and oxidative stress by regulating the NF-κB/MAPK signaling pathway in deoxynivalenol-challenged piglets. Environ Pollut. 2021; 289:117865.

Tian L, Ri H, Qi J, Fu P. Berberine elevates mitochondrial membrane potential and decreases reactive oxygen species by inhibiting the Rho/ROCK pathway in rats with diabetic encephalopathy. Mol Pain. 2021; 17:1744806921996101.

Tian W, Hao H, Chu M, Gong J, Li W, Fang Y, et al. Berberine suppresses lung metastasis of cancer via inhibiting endothelial transforming growth factor beta receptor 1. Front Pharmacol. 2022;13:917827.

Vita AA, Aljobaily H, Lyons DO, Pullen NA. Berberine delays onset of collagen-induced arthritis through T cell suppression. Int J Mol Sci. 2021;22 (7):3522.

Waly H, Abd-Elkareem M, Raheem S, Abou Khalil NS. Berberine protects against diclofenac sodium-induced testicular impairment in mice by its antioxidant and anti-apoptotic activities. Iran J Basic Med Sci. 2022;25(6):767.

Wang M, Geng X, Li K, Wang Y, Duan X, Hou C, et al. Berberine ameliorates mesenteric vascular dysfunction by modulating perivascular adipose tissue in diet-induced obese in rats. BMC Complement Med Ther. 2022;22(1):198.

Wang Y, Tong Q, Ma SR, Zhao ZX, Pan LB, Cong L, et al. Oral berberine improves brain dopa/dopamine levels to ameliorate Parkinson's disease by regulating gut microbiota. Signal Transduct Target Ther. 2021; 6(1):77.

Wen L, Han Z, Li J, Du Y. c-MYC and HIF1α promoter G-quadruplexes dependent metabolic regulation mechanism of berberine in colon cancer. J Gastrointest Oncol. 2022;13(3):1152.

Wolf PG, Devendran S, Doden HL, Ly LK, Moore T, Takei H, et al. Berberine alters gut microbial function through modulation of bile acids. BMC Microbiol. 2021;21(1):24.

Wu Y, Chen Q, Wen B, Wu N, He B, Chen J. Berberine reduces Aβ42 deposition and tau hyperphosphorylation via ameliorating endoplasmic reticulum stress. Front Pharmacol. 2021;12:640758.

Xia S, Ma L, Wang G, Yang J, Zhang M, Wang X, et al. In vitro antimicrobial activity and the mechanism of berberine against methicillin-resistant Staphylococcus aureus isolated from bloodstream infection patients. Infect Drug Resist. 2022;15:1933-44.

Xiang XY, Liu T, Wu Y, Jiang XS, He JL, Chen XM, et al. Berberine alleviates palmitic acid-induced podocyte apoptosis by reducing reactive oxygen species-mediated endoplasmic reticulum stress. Mol Med Rep. 2021;23(1):3.

Xie P, Ren ZK, Lv J, Hu YM, Guan ZZ, Yu WF. Berberine ameliorates oxygen-glucose deprivation/ reperfusion-induced apoptosis by inhibiting endoplasmic reticulum stress and autophagy in PC12 cells. Curr Med Sci. 2020;40:1047-56.

Xie W, Su F, Wang G, Peng Z, Xu Y, Zhang Y, et al. Glucose-lowering effect of berberine on type 2 diabetes: A systematic review and meta-analysis. Front Pharmacol. 2022;13:4734.

Xie Z, Liu X, Huang X, Liu Q, Yang M, Huang D, et al. Remodelling of gut microbiota by Berberine attenuates trimethylamine N-oxide-induced platelet hyperreaction and thrombus formation. Eur J Pharmacol. 2021;911:174526.

Xu Y, Yu T, Ma G, Zheng L, Jiang X, Yang F, et al. Berberine modulates deacetylation of PPARγ to promote adipose tissue remodeling and thermogenesis via AMPK/SIRT1 pathway. Int J Biol Sci. 2021;17 (12):3173.

Yan S, Chang J, Hao X, Liu J, Tan X, Geng Z, et al. Berberine regulates short-chain fatty acid metabolism and alleviates the colitis-associated colorectal tumorigenesis through remodeling intestinal flora. Phytomedicine. 2022;102:154217.

Yang KT, Chao TH, Wang IC, Luo YP, Ting PC, Lin JH, et al. Berberine protects cardiac cells against ferroptosis. Tzu Chi Med J. 2022;34(3):310.

Yang L, Cao J, Wei J, Deng J, Hou X, Hao E, et al. Antiproliferative activity of berberine in HepG2 cells via inducing apoptosis and arresting cell cycle. Food Funct. 2021;12:12115-26.

Yarmohammadi F, Hayes AW, Karimi G. The therapeutic effects of berberine against different diseases: A review on the involvement of the endoplasmic reticulum stress. Phytother Res. 2022;36: 3215-31.

Ye Y, Liu X, Wu N, Han Y, Wang J, Yu Y, et al. Efficacy and safety of berberine alone for several metabolic disorders: a systematic review and meta-analysis of randomized clinical trials. Front Pharmacol. 2021;12:653887.

Ye Z, Wang Q, Dai S, Ji X, Cao P, Xu C, et al. The Berberis vulgaris L. extract berberine exerts its antioxidant effects to ameliorate cholesterol overloading–induced cell apoptosis in the primary mice hepatocytes: an in vitro study. In Vitro Cell Dev Biol Anim. 2022; 58:855-66.

Yi J, Wu S, Tan S, Qin Y, Wang X, Jiang J, et al. Berberine alleviates liver fibrosis through inducing ferrous redox to activate ROS-mediated hepatic stellate cells ferroptosis. Cell Death Discov. 2021;7(1):374.

Yin Z, Tan R, Yuan T, Chen S, Quan Y, Hao Q, et al. Berberine prevents diabetic retinopathy through inhibiting HIF-1α/VEGF/NF-κ B pathway in db/db mice. Pharmazie. 2021;76:165-71.

Yu M, Alimujiang M, Hu L, Liu F, Bao Y, Yin J. Berberine alleviates lipid metabolism disorders via inhibition of mitochondrial complex I in gut and liver. Int J Biol Sci. 2021;17(7):1693.

Zhai J, Li Z, Zhang H, Ma L, Ma Z, Zhang Y, et al. Berberine protects against diabetic retinopathy by inhibiting cell apoptosis via deactivation of the NF-κB signaling pathway. Mol Med Rep. 2020a;22:4227-35.

Zhai L, Huang T, Xiao HT, Wu PG, Lin CY, Ning ZW, et al. Berberine Suppresses colonic inflammation in dextran sulfate sodium–induced murine colitis through inhibition of cytosolic phospholipase A2 activity. Front Pharmacol. 2020b;11:576496.

Zhang M, Liu J, Yu C, Tang S, Jiang G, Zhang J, et al. Berberine Regulation of cellular oxidative stress, apoptosis and autophagy by modulation of m6A mRNA methylation through targeting the Camk1db/ERK pathway in zebrafish-hepatocytes. Antioxidants (Basel). 2022a;11(12):2370.

Zhang M, Yang H, Yang E, Li J, Dong L. Berberine decreases intestinal GLUT2 translocation and reduces intestinal glucose absorption in mice. Int J Mol Sci. 2022b;23(1):327.

Zhao Z, Zeng J, Guo Q, Pu K, Yang Y, Chen N, et al. Berberine suppresses stemness and tumorigenicity of colorectal cancer stem-like cells by inhibiting m6A methylation. Front Oncol. 2021;11:775418.

Zheng C, Wang Y, Xu Y, Zhou L, Hassan S, Xu G, et al. Berberine inhibits dendritic cells differentiation in DSS-induced colitis by promoting Bacteroides fragilis. Int Immunopharmacol. 2021a;101:108329.

Zheng Y, Kou J, Wang P, Ye T, Wang Z, Gao Z, et al. Berberine-induced TFEB deacetylation by SIRT1 promotes autophagy in peritoneal macrophages. Aging (Albany NY). 2021b;13(5):7096.

Zhu C, Huang K, Bai Y, Feng X, Gong L, Wei C, et al. Dietary supplementation with berberine improves growth performance and modulates the composition and function of cecal microbiota in yellow-feathered broilers. Poult Sci. 2021;100:1034-48.

Zhu C, Li K, Peng XX, Yao TJ, Wang ZY, Hu P, et al. Berberine a traditional Chinese drug repurposing: Its actions in inflammation-associated ulcerative colitis and cancer therapy. Front Immunol. 2022;13:1083788.